REMARKS

Consideration of the present application in view of the above amendments and the following remarks is respectfully requested. As noted above, claims 1-11 have been cancelled without prejudice to the filing of any divisional, continuation, or continuation-in-part application. New claims 12 to 53 have been added to more specifically claim certain embodiments of the invention. Applicant respectfully submits that new claim 12 essentially corresponds to original claim 1 and new claim 27 essentially corresponds to original claim 5. Support for the new claims may be found, in part, in the specification at page 7, line 25 through page 8, line 18; and Example 1 (*see, e.g.*, claims 12-29 and 37-47); at page 2, lines 17-30; and Example 6 (*see, e.g.*, claims 12, 27, 30-36, and 37-47); and at page 12, line 14 through page 13, line 3; and Examples 3-5 and 7 (*see, e.g.*, claims 12-14, 27-29, and 48-53). No new matter has been added. Therefore, new claims 12-53 are now pending.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The first of the attached pages is captioned "Version with Markings to Show Changes Made."

The following comments with regard to the prior Office Action dated February 16, 2000 (Paper No. 15), which incorporates by reference the Office Action dated May 26, 1999 (Paper No. 11), are provided for the Examiner's convenience in evaluating the new claims.

PRIOR REJECTIONS UNDER 35 U.S.C. § 102(b)

(1) In the Office Action dated February 16, 2000, claims 1, 5 and 9-11 were rejected under 35 U.S.C. § 102(b) as anticipated by Dale *et al.* (*J. Immunol. 151*:2188, 1993) or Dale *et al.* (*Vaccine 14*:944, 1996). In particular, it is alleged that these references teach recombinant multivalent group A streptococcal vaccines that have tandemly ligated peptides or peptides covalently linked to KLH, either of which would generate a non-immunogenic C-terminus for the immunogenic polypeptide.

Applicant respectfully traverses this ground of rejection and submits that both Dale *et al.* (1993) and Dale *et al.* (1996) fail to meet every limitation of the instant claims and,

therefore, fail to anticipate the claimed invention. As disclosed in the specification and recited in the new claims, the present invention is directed in pertinent part, for this rejection, to methods and compositions of a recombinant fusion polypeptide having an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. As discussed in greater detail below, Applicant respectfully submits that Dale *et al.* (1993) and Dale *et al.* (1996) fail to disclose a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci.

Dale *et al.* (1993) merely disclose a "fusion polypeptide" consisting of four different peptides (*i.e.*, referred to as a multivalent hybrid molecule), all of which are "immunogenic peptides" (*see, e.g.*, Dale, 1993, at page 2189, column 1, lines 12-26). Therefore, Dale *et al.* (1993), while teaching a fusion polypeptide consisting of an "immunogenic portion," fail to teach or suggest a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. Moreover, Dale *et al.* (1993) teach hybrid molecules having a C-terminal "immunogenic peptide" that failed to elicit a strong antibody response (*see, e.g.*, Dale *et al.*, 1993 at page 2192, Table II). Applicant respectfully submits that the reason the C-terminal "immunogenic peptide" had reduced immunogenicity was likely due to the *lack* of a protective C-terminal peptide added to the immunogenic portion of the fusion polypeptide. Hence, Dale *et al.* (1993) fail to provide a recombinant fusion polypeptide having an immunogenic portion *and* a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci.

Similarly, Dale *et al.* (1996) merely disclose another "fusion polypeptide" consisting only of an "immunogenic portion." Hence, Dale *et al.* also fail to teach or suggest a

C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci (*see, e.g.*, Dale *et al.*, 1996 at page 947, Table 1). Furthermore, Applicant respectfully submits that Dale *et al.* (1996) does not disclose a fusion polypeptide covalently linked to KLH, but rather teaches a *single* peptide covalently coupled to KLH (*see, e.g.*, Dale *et al.*, 1996 at page 945, column 2, section titled "Identification of opsonic epitopes of type 2 and type 3 M proteins"). Additionally, the covalent linkage of KLH to the peptide is random and not necessarily at the C-terminal end. Thus, the KLH modified peptide of Dale *et al.* (1996) does not have an immunogenic portion comprising *at least two* immunogenic peptides and does not have a C-terminal peptide which protects the immunogenicity of the immunogenic portion. Consequently, Dale *et al.* (1993) and Dale *et al.* (1996) both fail to teach a recombinant fusion polypeptide having an immunogenic portion and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci, as provided by the presently claimed invention.

Accordingly, Applicant respectfully submits that claims 1, 5 and 9-11, as well as new claims 12, 27, 30, 31, and 48, distinguish patentably over Dale *et al.* (1993) and Dale *et al.* (1996) and, therefore, satisfy the requirements of 35 U.S.C. § 102(b).

(2) In the Office Action, claims 5 and 6 were rejected under 35 U.S.C. § 102(b) as anticipated by Dale and Beachey (*J. Exp. Med. 163*:1191, 1986). In particular, it is alleged that the Dale and Beachey teach a multivalent serotype 5 Group A Streptococcal vaccine which has at least two immunogenic peptides more than 10 amino acids in length. It is further alleged that multivalent peptides covalently linked to KLH would have a non-immunogenic C-terminus for the immunogenic polypeptide.

Applicant respectfully traverses this ground of rejection and submits that Dale and Beachey fail to meet every limitation of the instant claims and, therefore, fail to anticipate the claimed invention. As disclosed in the specification and recited in the new claims, the present invention is directed in pertinent part, for this rejection, to a composition for promoting an immune response against Group A Streptococci comprising (1) a recombinant fusion polypeptide

having an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci; and (2) a pharmaceutically acceptable excipient or diluent. Specifically, Dale and Beachey merely teach the synthesis of *individual* serotype 5 M protein peptides and determine the immunogenicity of each *individual* peptide that was covalently linked to either tetanus toxoid or KLH. Moreover, it is conceded that Dale and Beachey fail to "teach making immunogenic fusion polypeptides" (*see* Office Action Paper No. 11, dated May 26, 1999, at page 7, paragraph 2). Thus, Dale and Beachey fail to teach a recombinant fusion polypeptide, much less a recombinant fusion polypeptide having an immunogenic portion and a C-terminal peptide which protects the immunogenicity of the immunogenic portion.

Furthermore, Applicant respectfully submits that the random conjugation of tetanus toxoid or KLH to the serotype 5 M protein peptides is beside the point. Even assuming, *arguendo*, that the Dale and Beachey disclose multivalent peptides, a person having ordinary skill in the art would readily appreciate that a chemically conjugated molecule is structurally dissimilar and, therefore, not the same as a recombinant fusion protein. Likewise, a person having ordinary skill in the art would know that the conjugation reaction results in random cross-linking and not in a "fusion polypeptide" having a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci as described in the specification and recited in the claims. Indeed, it is conceded that a fusion polypeptide provides a "known and disclosed advantage of [over a chemically synthetic polypeptide] high accuracy peptide sequence, reproducibility, and...unlimited supply of reagent" (*see* Office Action Paper No. 11, dated May 26, 1999, at page 8, lines 1-2). Additionally, the ordinary meaning of a "fusion polypeptide" is not found in Meriam Webster's Collegiate Dictionary, as alleged in the Office Action, but in a scientific dictionary or textbook that a person having ordinary skill would consult (*see, e.g.*, the definition of "fusion protein" in Weaver and Hedrick, Genetics, Ed. Kane, 1989; copy enclosed). Applicant respectfully submits,

therefore, that the term "recombinant" (*see, e.g.*, specification at page 9, line 30 through page 10, line 8; and at page 10, lines 24-26) as recited in the new claims is redundant to the recited term "fusion polypeptide," and is present for mere formality (*i.e.*, not for reasons of patentability) so as to expedite the prosecution of this application.

Accordingly, Applicant respectfully submits that claims 5 and 6, as well as new claims 27 and 42, distinguish patentably over Dale and Beachey and, therefore, satisfy the requirements of 35 U.S.C. § 102(b).

(3) In the Office Action, claims 5 and 7 were rejected under 35 U.S.C. § 102(b) as anticipated by Beachey and Seyer (*J. Immunol. 136*:2287, 1986). In particular, it is alleged that Beachey and Seyer teach a multivalent serotype 6 Group A Streptococcal vaccine which has at least two immunogenic peptides more than 10 amino acids in length. It is further alleged that a conjugated tetanus toxoid would act as a protective, non-immunogenic peptide C-terminal to the immunogenic polypeptide.

Applicant respectfully traverses this ground of rejection and submits that Beachey and Seyer fail to meet every limitation of the instant claims and, therefore, fail to anticipate the claimed invention. As disclosed in the specification and recited in the new claims, the present invention is directed in pertinent part, for this rejection, to a composition for promoting an immune response against Group A Streptococci comprising (1) a recombinant fusion polypeptide having an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci; and (2) a pharmaceutically acceptable excipient or diluent. Similar to Dale and Beachey, Beachey and Seyer merely teach the synthesis of *individual* serotype 6 M protein peptides and determine the immunogenicity of each *individual* peptide. Furthermore, the addition of the tetanus toxoid fails to result in a recombinant fusion polypeptide and, consequently, does not cure the aforementioned deficiency. Moreover, it is conceded that Beachey and Seyer fail to "teach making immunogenic fusion polypeptides" (*see* Office Action

Paper No. 11, dated May 26, 1999, at page 8, last paragraph). Thus, Beachey and Seyer fail to teach a recombinant fusion polypeptide, fail to teach an immunogenic portion comprising *at least two* immunogenic peptides, and fail to teach a C-terminal peptide which protects the immunogenicity of the immunogenic portion, as provided by the presently claimed invention.

Accordingly, Applicant respectfully submits that claims 5 and 7, as well as new claims 27 and 44, distinguish patentably over Beachey and Seyer and, therefore, satisfy the requirements of 35 U.S.C. § 102(b).

PRIOR REJECTIONS UNDER 35 U.S.C. § 103(a)

(1) In the Office Action, claims 1 and 2 were rejected under 35 U.S.C. § 103(a) as obvious over Dale and Beachey (*J. Exp. Med. 163*:1191, 1986) and Dale *et al.* (*J. Immunol. 151*:2188, 1993). In particular, it is alleged that it would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to use the Dale and Beachey immunogenic peptide from serotype 5 Group A Streptococci in the method of Dale *et al.* (1993) to make an immunogenic fusion polypeptide from serotype 5 Group A Streptococci to attain the known and disclosed advantage of a fusion protein, including high accuracy peptide sequence, reproducibility, and an unlimited supply of reagent.

Applicant respectfully traverses this ground of rejection and submits that Dale and Beachey and Dale *et al.* (1993), taken alone or in combination, fail to teach or suggest the claimed invention and, further, would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success. As noted above, the present invention is directed in pertinent part, for this rejection, to a recombinant fusion polypeptide having an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. As also noted above, Dale and Beachey concededly fail to teach or suggest a recombinant fusion polypeptide, an immunogenic portion comprising *at least two*

immunogenic peptides, and a C-terminal peptide which protects the immunogenicity of the immunogenic portion.

Furthermore, Applicant respectfully submits that Dale *et al.* (1993) fail to remedy the deficiencies of Dale and Beachey because Dale *et al.* (1993), while teaching a recombinant fusion polypeptide having an immunogenic portion *only*, fail to teach or suggest a recombinant fusion polypeptide *also* having a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. Additionally, Dale *et al.* (1993) disclose serotype 5 Group A Streptococci, as does Dale and Beachey, and, therefore, is merely cumulative prior art.

Additionally, not only would Dale and Beachey and Dale *et al.* (1993) not motivate a person having ordinary skill in the art to make and use the claimed invention, Applicant respectfully submits that Dale *et al.* (1993), in fact, teach away from the present invention. In particular, Dale *et al.* (1993) recognize the reduced ability of the C-terminal "immunogenic peptide" to elicit antibodies and, therefore, suggest enhancing the immunogenicity of the immunogenic peptides by modifying the length and/or changing the conformation of the regions that link the immunogenic peptides together (*see*, Dale *et al.*, 1993, at page 2193, column 1, paragraph 2). Although, as noted in the Office Action (Paper No. 11), the prior art teaches some advantages of a recombinant fusion polypeptide, such as a high accuracy peptide sequence, reproducibility, and unlimited supply of reagent, the prior art fails to teach or suggest a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci, as provided by the specification and recited in the claims. Therefore, Applicant respectfully submits that Dale and Beachy, taken alone or in view of Dale *et al.* (1993), fail to convey to a person having ordinary skill in the art a reasonable expectation of success if the prior art were modified according to the instant invention.

Accordingly, Applicant respectfully submits that claims 1 and 3, as well as new claims 12 and 42, distinguish patentably over Dale and Beachy and Dale *et al.* (1993), taken

alone or in combination, and that the present invention satisfies the requirements of 35 U.S.C. § 103(a).

(2) In the Office Action, claims 1 and 3 were rejected under 35 U.S.C. § 103(a) as obvious over Beachey and Seyer (*J. Immunol. 136*:2287, 1986) and Dale *et al.* (*J. Immunol. 151*:2188, 1993). In particular, it is alleged that it would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to use the Beachey and Seyer immunogenic peptide from serotype 6 Group A Streptococci in the method of Dale *et al.* (1993) to make an immunogenic fusion polypeptide from serotype 5 Group A Streptococci to attain the known and disclosed advantage of a fusion protein, including high accuracy peptide sequence, reproducibility, and an unlimited supply of reagent.

Applicant respectfully traverses this ground of rejection and submits that Beachey and Seyer and Dale *et al.* (1993), taken alone or in combination, fail to teach or suggest the claimed invention and, further, would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success. As noted above, the present invention is directed in pertinent part, for this rejection, to a recombinant fusion polypeptide having an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. As also noted above, Beachey and Seyer concededly fail to teach or suggest a recombinant fusion polypeptide, an immunogenic portion comprising *at least two* immunogenic peptides, and a C-terminal peptide which protects the immunogenicity of the immunogenic portion. Additionally, Dale *et al.* (1993) disclose serotype 6 Group A Streptococci, as does Beachey and Seyer, and, therefore, is merely cumulative prior art. Therefore, Applicant respectfully submits that Beachey and Seyer and Dale *et al.* (1993), taken alone or in combination, fail to provide a reasonable expectation of success and fail to teach or suggest all of the claim limitations to a person having ordinary skill in the art.

Accordingly, Applicant respectfully submits that claims 1 and 3, as well as new claims 12 and 44, distinguish patentably over Beachey and Seyer and Dale *et al.* (1993), taken alone or in combination, and that the present invention satisfies the requirements of 35 U.S.C. § 103(a).

---

(3) In the Office Action, claims 1 and 4 were rejected under 35 U.S.C. § 103(a) as obvious over Dale *et al.* (*J. Immunol. 151*:2188, 1993) and Beall *et al.* (*J. Clin. Microbiol. 34*:953, 1996). In particular, it is alleged that it would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to substitute immunoprotective M proteins from the Beall *et al.* serotypes 1, 1.1, 2-4, 11-14, 18-19, 22, 28, 30, 48, 52, and 56 of Group A Streptococci for the serotype 5 taught by Dale *et al.* (1993) to make vaccines against medically important serotypes of Group A Streptococci.

Applicant respectfully traverses this ground of rejection and submits that Beall *et al.* and Dale *et al.* (1993), taken alone or in combination, fail to teach or suggest the claimed invention and, further, would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success. As noted above, the present invention is directed in pertinent part, for this rejection, to a recombinant fusion polypeptide having an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. In particular, Beall *et al.* teach the use of the polymerase chain reaction as a tool to determine the M protein type of clinical Group A Streptococcal isolates, but do not teach or suggest the use of M protein fragments as immunogenic peptides, much less a recombinant fusion polypeptide having an immunogenic portion and a C-terminal peptide which protects the immunogenicity of the immunogenic portion.

Dale *et al.* (1993) fail to remedy this deficiency because Dale *et al.* (1993), while teaching a fusion polypeptide having *only* an immunogenic portion, also fail to teach or suggest a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the

C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. Furthermore, as noted above and in the Office Action (Paper No. 11), Beall *et al.* merely disclose several serologic M types from Group A Streptococci and nothing more, which would not motivate a person of ordinary skill in the art to combine the teachings of Beall *et al.* and Dale *et al.* (1993) to arrive at the instant invention. Moreover, the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see In re Mills*, 16 USPQ2d 1430, Fed. Cir., 1990).

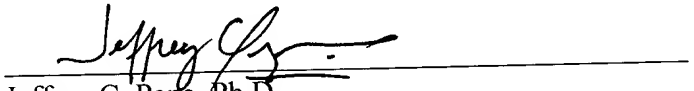
Accordingly, Applicant respectfully submits that claims 1 and 4, as well as new claims 12 and 15, are readily distinguished over Beall *et al.* and Dale *et al.* (1993), taken alone or in combination, and that the present invention satisfies the requirements of 35 U.S.C. § 103(a).

In summary, Applicant respectfully submits that a *prima facie* case of obviousness has not been established. In particular, the cited prior art fails to teach or suggest a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. Further, the cited prior art only teach a fusion polypeptide, where a fusion polypeptide is disclosed at all, consisting *solely* of an "immunogenic portion." Therefore, the cited prior art, taken alone or in combination, fail to provide a reasonable expectation of success and fail to teach or suggest all of the claim limitations to a person having ordinary skill in the art. Accordingly, Applicant respectfully submits that the presently claimed invention satisfies the requirements of 35 U.S.C. § 103(a).

All of the claims pending in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions on this matter.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



Jeffrey C. Pepe, Ph.D.
Registration No. 46,985

JCP:brg

Enclosures:

Postcard
Check for $1305
PTO Transmittal Form
PTO Fee Transmittal Form (+ copy)

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

WPN\481112\410\Forms\410PreAm

Application No. : 09/151,409

Docket No. : 481112.410

Examiner : Li Lee, M.D., Ph.D.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 2, line 4, has been amended as follows:

Briefly stated, the present invention provides immunogenic synthetic fusion polypeptides which stimulate an immune response against Group A streptococci. Within one aspect such polypeptides comprise (a) at least two immunogenic ~~polypetides~~ polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating an immune response against Group A streptococci, and a peptide C terminal to the immunogenic polypeptide which protects the immunogenicity of the immunogenic portion. Within preferred embodiments, the C-terminal peptide is not required to stimulate an immune response against Group A streptococci and hence, may be an inconsequential non-immunogenic peptide, or a reiterated immunogenic polypeptide. Within certain embodiments, the immunogenic polypeptide can be obtained from a wide variety of Group A streptococci (ranging from "1" to greater than "90"), including for example, Types 1, 1.1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52, 55 and 56.

Paragraph beginning at page 2, line 17 has been amended as follows:

Within other aspects of the present invention, vaccinating agents are provided for promoting an immune response against Group A streptococci, comprising (a) at least two immunogenic ~~polypetides~~ polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating a protective immune response against Group A streptococci, and (b) a peptide C terminal to the immunogenic polypeptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is not required to stimulate an immune response against Group A streptococci. As above, the polypeptide may be

selected from a wide variety of Group A streptococci (ranging from "1" to greater than "90"), including for example, types 1.1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52, 55 and 56. Within certain further embodiments, the vaccinating agent may further comprise an adjuvant, such as, for example, alum, Freund's adjuvant, and/or an immunomodulatory cofactor (*e.g.*, IL-4, IL-10, γ-IFN, or IL-2, IL-12 or IL-15).

Paragraph beginning at page 5, line 4, has been amended as follows:

As noted above, the present invention provides vaccinating agents suitable for preventing Group A streptococcal infections. Briefly, as described in more detail below it has been discovered that, in order to optimize the immunogenicity of all aspects of a multivalent vaccine. Within one aspect of the invention, immunogenic synthetic fusion polypeptides which stimulate an immune response against Group A streptococci are provided. Such polypeptides generally comprise (a) at least two immunogenic ~~polypetides~~ polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating an immune response against Group A streptococci, and (b) a peptide C terminal to the immunogenic polypeptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is not required to stimulate an immune response against Group A streptococci. Particularly preferred protective peptides are generally at least ten amino acids in length, and may be 30 amino acids or longer.

Paragraph beginning at page 18, line 26, has been amended as follows:

Opsonic M protein antibodies correlate with protection against infection with the same serotype of group A streptococci (Lancefield, R.C., "Current knowledge of the type specific M antigens of group A streptococci," *J. Immunol. 89*:307-313, 1962; Lancefield, R.C., "Persistence of type-specific antibodies in man following infection with group A streptococci," *J. Exp. Med. 110*:271-282, 1959). Two related in vitro assays are used to detect opsonic antibodies in immune sera. The first is a screening assay that measures opsonization in mixtures of immune serum, whole, nonimmune human blood and the test organism (Beachey et al., "Purification and properties of M protein extracted from group A streptococci with pepsin: Covalent structure of the amino terminal region of the type 24 M antigen," *J. Exp. Med. 145*:1469-1483, 1977). 0.1 ml

of test serum is added to a standard number of bacteria and incubated for 15 minutes at room temperature. 0.4 ml of lightly heparinized human blood is added and the entire mixture is rotated end-over-end at ~~370~~ 37°C for 45 minutes. At the end of the rotation, smears are prepared on microscope slides that are air-dried and stained with Wright's stain. "Percent opsonization" is quantitated by counting the percentage of polymorphonuclear leukocytes that have ingested or are associated with bacteria. An interpretable assay must have a preimmune control value that is 10% opsonization or less.

Paragraph beginning at page 19, line 15, has been amended as follows:

Confirmation of the presence of opsonic antibodies is obtained by indirect bactericidal antibody assays according to the original description by Lancefield (Lancefield, R.C., "Current knowledge of the type specific M antigens of group A streptococci," *J. Immunol. 89*:307-313, 1962). This assay is performed using test mixtures as described above except that fewer bacteria are added and the rotation is allowed to proceed for 3 hours. At the end of the rotation, pour plates are made in sheep blood agar and bacteria surviving are quantitated after overnight growth at ~~370~~ 37°C. Percent killing in the presence of immune serum is calculated by comparing to the growth in nonimmune serum.

Paragraph beginning at page 19, line 29, has been amended as follows:

Protective efficacy of M protein vaccines is determined by either indirect or direct (passive or active immunization) mouse protection tests. Indirect tests are performed by giving mice 1 ml of immune or preimmune serum via the intraperitoneal (i.p.) route 24 hours prior to challenge infections with the test organism given i.p. (Beachey et al., "Human immune response to immunization with a structurally defined polypeptide fragment of streptococcal M protein," *J. Exp. Med. 150*:862-877, 1979). For each test organism, groups of 25 mice receive either preimmune ~~of~~ or immune serum. The animals are then divided into 5 groups of 5 mice each and 10-fold increasing challenge doses of virulent streptococci are given to each subgroup. After 7 days of observation, the LD50 is calculated for each serotype tested.

Paragraph beginning at page 21, line 17, has been amended as follows:

To assure that none of the M protein vaccines evokes tissue-crossreactive antibodies, indirect immunofluorescence assays are performed using frozen sections of human heart, kidney, and brain (Dale, J.B. and Beachey E.H., "Protective antigenic determinant of streptococcal M protein shared with sarcolemmal membrane protein of human heart," *J. Exp. Med. 156*:1165-1176, 1982). Thin sections of tissue obtained at autopsy (4um) are prepared on microscope slides and stored in a sealed box at ~~-700C~~ -70°C until use. Test serum is diluted 1:5 in PBS and dropped onto the tissue section. Control slides are made with preimmune serum and PBS. The slides are incubated at ambient temperature for 30 minutes and then washed three times in PBS in a slide holder. Fluorescein-labeled goat anti-IgG/IgM/IgA is diluted 1:40 in PBS and dropped onto the slides which are again washed, dried, and mounted with 1% Gelvetol and a coverslip. Fluorescence is detected using a Zeiss Axiophot microscope equipped with a xenon light source. Immunofluorescence is recorded using a scale of 0-4+, with 0 being no fluorescence and 4+ being that obtained with a standard, positive antiserum raised in rabbits against whole type 5 M protein (Dale, J.B. and Beachey, E.H., "Multiple heart-cross-reactive epitopes of streptococcal M proteins," *J. Exp. Med. 161*:113-122, 1985).

Paragraph beginning at page 22, line 14, has been amended as follows:

Three rabbits each were immunized with 100 ~~ug~~ µg doses of the hexavalent vaccine in either alum ~~of~~ or CFA. Booster injections of the same dose were given at 4 and 8 weeks in either alum or saline, respectively. ELISA titers were determined using the purified hexavalent protein as the solid phase antigen (Figure 3). Sera from the animals that received the hexavalent vaccine in alum had antibody titers that were equal to or greater than the sera from rabbits that received the same dose in CFA. In a subsequent experiment, three rabbits were immunized I.M. with 100 ~~ug~~ µg of the hexavalent vaccine in saline alone according to the same schedule. None of these rabbits developed significant antibody titers against either the immunogen or the respective pep M proteins (data not shown). These data indicate that alum is a suitable and necessary adjuvant for the multivalent vaccine and is equal to the adjuvant activity of CFA in combination with the hexavalent protein.

In the Claims:

Claims 1-11 have been canceled without prejudice.

New claims 12-53 have been added as follows:

12. A recombinant fusion polypeptide, comprising:

(a) an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(b) a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci.

13. The polypeptide according to claim 12 wherein the C-terminal peptide is a reiteration of at least one of the immunogenic peptides.

14. The polypeptide according to claim 12 wherein the C-terminal peptide is a peptide from another pathogen.

15. The polypeptide according to any one of claims 12-14 wherein at least one of the immunogenic peptides is from a Group A Streptococci serotype selected from the group consisting of 1, 1.1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52 and 56.

16. The polypeptide according to claim 15 wherein the immunogenic portion comprises six immunogenic peptides.

17. The polypeptide according to any one of claims 12-14 wherein at least one of the immunogenic peptides is from a serotype 1 Group A Streptococci.

18. The polypeptide according to claim 17 wherein the immunogenic portion comprises six immunogenic peptides.

19. The polypeptide according to any one of claims 12-14 wherein at least one of the immunogenic peptides is from a serotype 4 Group A Streptococci.

20. The polypeptide according to claim 19 wherein the immunogenic portion comprises six immunogenic peptides.

21. The polypeptide according to any one of claims 12-14 wherein at least one of the immunogenic peptides is from a serotype 5 Group A Streptococci.

22. The polypeptide according to claim 21 wherein the immunogenic portion comprises six immunogenic peptides.

23. The polypeptide according to any one of claims 12-14 wherein at least one of the immunogenic peptides is from a serotype 6 Group A Streptococci.

24. The polypeptide according to claim 23 wherein the immunogenic portion comprises six immunogenic peptides.

25. The polypeptide according to any one of claims 12-14 wherein at least one of the immunogenic peptides is from a serotype 12 Group A Streptococci.

26. The polypeptide according to claim 25 wherein the immunogenic portion comprises six immunogenic peptides.

27. A composition for promoting an immune response against Group A Streptococci, comprising:

(a) a recombinant fusion polypeptide, comprising:

(i) an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(ii) a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is in addition to the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci; and

(b) a pharmaceutically acceptable excipient or diluent.

28. The composition according to claim 27 wherein the C-terminal peptide is a reiteration of at least one of the immunogenic peptides.

29. The composition according to claim 27 wherein the C-terminal peptide is a peptide from another pathogen.

30. The composition according to any one of claims 27-29, further comprising an adjuvant.

31. The composition according to claim 30 wherein the adjuvant is alum or Freund's adjuvant.

32. The composition according to any one of claims 27-29, further comprising an immunomodulatory cofactor.

33. The composition according to claim 30, further comprising an immunomodulatory cofactor.

34. The composition according to claim 32 wherein the immunomodulatory cofactor is selected from the group consisting of IL-4, IL-10, γ-IFN, IL-2, IL-12, and IL-15.

35. The composition according to claim 33 wherein the immunomodulatory cofactor is selected from the group consisting of IL-4, IL-10, γ-IFN, IL-2, IL-12, and IL-15.

36. The composition according to any one of claims 27-29 wherein at least one of the immunogenic peptides is from a Group A Streptococci serotype selected from the group consisting of 1, 1.1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52 and 56.

37. The composition according to claim 36 wherein the immunogenic portion comprises six immunogenic peptides.

38. The composition according to any one of claims 27-29 wherein at least one of the immunogenic peptides is from a serotype 1 Group A Streptococci.

39. The composition according to claim 38 wherein the immunogenic portion comprises six immunogenic peptides.

40. The composition according to any one of claims 27-29 wherein at least one of the immunogenic peptides is from a serotype 4 Group A Streptococci.

41. The composition according to claim 40 wherein the immunogenic portion comprises six immunogenic peptides.

42. The composition according to any one of claims 27-29 wherein at least one of the immunogenic peptides is from a serotype 5 Group A Streptococci.

43. The composition according to claim 42 wherein the immunogenic portion comprises six immunogenic peptides.

44. The composition according to any one of claims 27-29 wherein at least one of the immunogenic peptides is from a serotype 6 Group A Streptococci.

45. The composition according to claim 44 wherein the immunogenic portion comprises six immunogenic peptides.

46. The composition according to any one of claims 27-29 wherein at least one of the immunogenic peptides is from a serotype 12 Group A Streptococci.

47. The composition according to claim 46 wherein the immunogenic portion comprises six immunogenic peptides.

48. A method for vaccinating a host against Group A Streptococci infections, comprising administering a composition according to any one of claims 27-29.

49. The method according to claim 48 wherein administering the composition elicits opsonic antibodies.

50. The method according to claim 48 wherein the opsonic antibodies do not cross-react with host tissue.

51. A method for vaccinating a host against Group A Streptococci infections, comprising administering a composition according to claim 30.

52. A method for vaccinating a host against Group A Streptococci infections, comprising administering a composition according to claim 33.

53. A method for vaccinating a host against Group A Streptococci infections, comprising administering a composition according to claim 37.